Epidemiology of Neural Tube Defects, Hawaii, 1986-1997

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Abstract

Neural tube defects (NTDs) in Hawaii between 1986 and 1997 were examined using data from a statewide birth defects surveillance system. The prevalence increased significantly over the twelve-year period. NTD prevalence did not appear to vary by place of residence. The relationship of type of defect, maternal age, and infant/fetus sex was similar to that reported in the literature.

Introduction

Neural tube defects (NTDs), a group of serious defects including anencephaly, spina bifida, and encephalocele, are one of the most common groups of birth defects in the United States, affecting approximately one in every 1,000 births each year.[1] Anencephaly is almost invariably fatal. Anencephalic infants who are not stillborn usually expire within several hours or days after birth. The prognosis of an infant with spina bifida depends upon the lesion's location and the presence of other defects. An infant with spina bifida often has some degree of limb paralysis or weakness and lack of bowel and bladder control. The lifetime direct and indirect costs for each person with spina bifida is estimated to be $300,000 (based on 1992 dollars), and the total medical costs for all individuals with spina bifida account for approximately $500 million each year.[2]

The etiology of NTDs has been studied extensively, but is still not completely understood. Both environmental and genetic factors are known to affect their prevalence. The recurrence risk for NTDs is 3-4 percent.[3] Racial/ethnic differences have been reported for NTDs, with the defects most common among Hispanics, followed by non-Hispanic whites, African-Americans, and Asians/Pacific Islanders.[4-10] The United States and other parts of the world have experienced a decline in the birth prevalence of NTDs over the last several decades.[4,5,11,12] Some of this decline in NTD prevalence may be attributed to the fact that, over the last several decades, prenatal screening of maternal serum alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol and antenatal diagnosis with ultrasound have allowed a proportion of fetuses with NTDs to be identified in utero and subsequently terminated, thus reducing the birth prevalence of NTDs.[13-15] However, this decline was reported prior to widespread prenatal screening and diagnosis and has been observed in areas where elective termination is not allowed.

NTDs rates can vary widely from state to state[5,13] and between regions within a state.[16] Reports of the influence of socioeconomic status on NTD risk have been mixed.[3] The risk for NTD has been found to be highest among the youngest and/or oldest maternal age groups.[4,7,17] Females are affected with NTDs more often than males.[3,6,11,12,18]

Maternal factors such as hyperthermia,[19] diabetes,[3,8] obesity,[20] and valproic acid use[3] have been associated with increased NTD risk. Investigations have reported that maternal use of alcohol,[3] caffeine,[21] oral contraceptives,[3] contraceptive spermicides,[22] ovulation-inducing drugs,[23] and recreational drugs[3] do not appear to influence NTD prevalence while exposure to glycol ethers,[24] radiation,[25] arsenic,[26] hazardous waste sites,[25,27] and drinking water contaminants[25] may increase NTD risk.

Maternal periconceptional consumption of folic acid (folate) has been found to reduce NTD risk by as much as seventy percent.[28] The exact mechanism through which this preventative effect operates is unclear, although homocysteine metabolism has been suggested .[29] In 1992, the U.S. Public Health Service recommended that all women who can become pregnant consume 0.4 mg of folic acid each day. And as of January 1, 1998, all "enriched" cereal grains were required by the U.S. Food and Drug Administration to be fortified with folic acid. However, the recommendation and other activities designed to increase public awareness of the importance of folic acid in reducing NTD risk have resulted in only slight increases in knowledge and folic acid consumption over initial low levels,[28] and it is too soon to evaluate the effectiveness of the fortification effort.

The purpose of this study was to examine the prevalence of various NTD diagnostic categories with respect to selected demographic factors such as year of delivery, infant/fetus sex and maternal race/ethnicity, age, and place of residence in Hawaii between 1986 and 1997.

Methods

Data were obtained from the Hawaii Birth Defects Program (HBDP), an active, population-based surveillance registry for birth defects for the entire state of Hawaii. The Program collects all pregnancies regardless of outcome (livebirth, fetal death, elective termination) and gestational age at the end of the pregnancy. Pregnancies of interest are ascertained from diagnostic code lists and other reports provided by all birth hospitals, facilities that perform elective

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This research was supported by a contract with the Hawaii State Department of Health, Children With Special Health Needs Branch, and grants from the Centers for Disease Control and Prevention, March of Dimes Birth Defects Foundation, Ronald McDonald Children s Charities, George F. Straub Trust, Queen Emma Foundation, Pacific Southwest Regional Genetics Network, and the Kamehameha Schools/Bishop Estate.

terminations due to fetal anomaly, tertiary care hospitals, and all clinics and laboratories in Hawaii that conduct prenatal diagnostic tests and genetic counseling. In addition to diagnostic information on each infant/fetus of interest, the HBDP collects data on demographic factors, health behaviors, and other medical information regarding the biological parents from the medical records.

The present study includes as cases all NTD-affected pregnancies which ended in Hawaii between 1986 and 1997, inclusive. Any cases where the diagnosis or place or type of pregnancy outcome could not be confirmed were excluded from the analysis. Data collected for each case included the type of NTD, end of pregnancy year, maternal race/ethnicity, maternal age, residence at delivery, and infant/fetus sex. Not all variables were available for every case, so the sum of cases reported for a given variable may not equal the total number of cases. Cases were sorted into diagnostic categories of anencephaly, spina bifida, encephalocele, and total NTDs. Any infant with more than one NTD was assigned to a single category in the following descending order of priority: anencephaly, spina bifida, encephalocele. No attempt was made to adjust for similar times of conception between the livebirths/fetal deaths and the elective terminations. Maternal race/ethnicity was assigned to one of four groups: white (excluding Hispanic), Far East Asian (Japanese, Chinese, Korean), Pacific Islander (Hawaiian, Samoan, Guamanian), and Filipino. Women with other or unknown race/ethnicity (n=24) were excluded from the analysis of this particular demographic factor. Women of mixed race/ethnicity were assigned to a single race/ethnicity according to the following rules: 1) If two races were noted and one was white, the other race was assigned; 2) If two or more races were listed and one was Hawaiian, the assigned race was Hawaiian; 3) If two or more races were listed and none of them was Hawaiian, the first race listed was assigned, unless it was white, in which case the second race was assigned.

The total prevalence for the twelve-year period and the prevalence by two-year interval of delivery per 10,000 livebirths and fetal deaths were calculated for each of the defect categories. For all other demographic factors, rates per 10,000 livebirths alone were calculated. Denominators were provided by the Hawaii State Department of Health, Office of Health Status Monitoring, as derived from birth and fetal death certificates. Secular trends were analyzed by the Chi-square tests for trend. Ninety-five percent confidence intervals were calculated by Poisson probability.

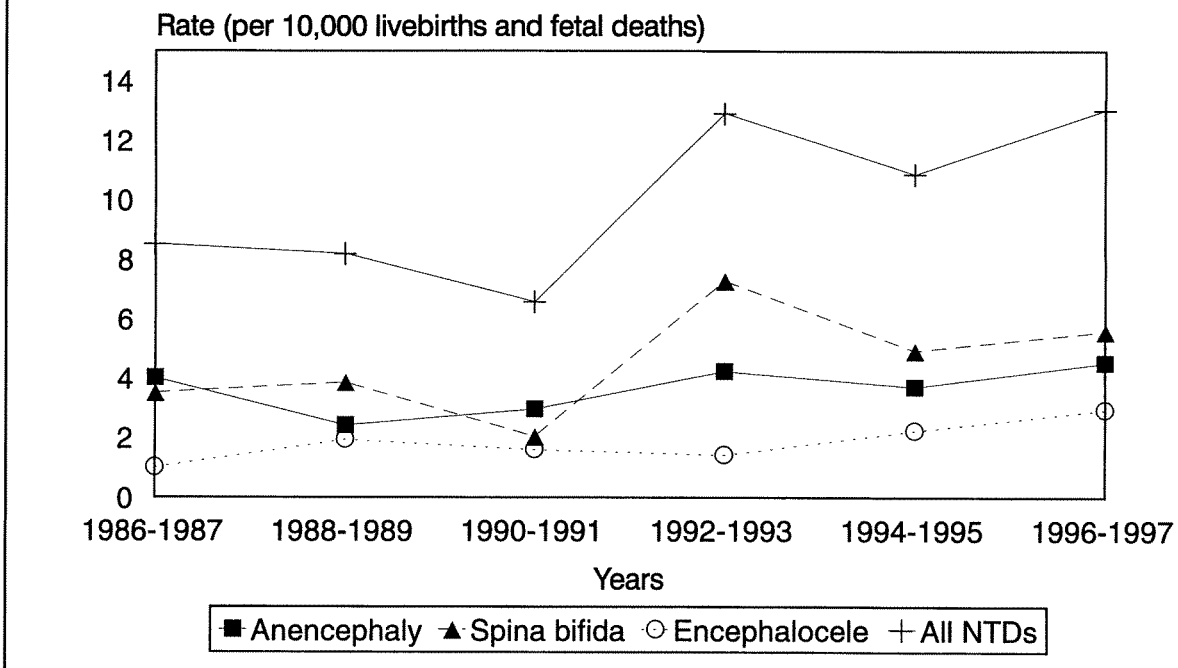
Results

Two hundred forty-five NTD-affected pregnancies were identified to have ended in Hawaii between 1986 and 1997, inclusive, for a prevalence of 9.95 (95 percent confidence interval (CI) 8.74-11.28) per 10,000 livebirths and fetal deaths. Of these cases, 89 (36.3 percent) were anencephaly, 111 (45.3 percent) spina bifida, and 45 (18.4 percent) encephalocele. The prevalence for anencephaly and spina bifida were similar (anencephaly 3.62, 95 percent CI 2.90-4.45; spina bifida 4.51, 95 percent CI 3.71-5.43), while the prevalence for encephalocele was significantly lower (1.83, 95 percent CI 1.33-2.45).

The rates of the various NTD diagnosis categories for each two-year interval of the study are presented in figure 1. The rates for all NTD categories increased over the twelve-year period of the study. This trend was not statistically significant for anencephaly (p=0.351), spina bifida (p=0.052), or encephalocele (p=0.138), but was statistically significant for all NTDs combined (p=0.012).

Table 1 shows the prevalence of NTDs by maternal race/ethnicity. The rate per 10,000 births for all NTDs combined was highest for Pacific Islanders (11.59), followed by whites (11.32), Far East Asians (9.81), and Filipinos (8.70). This pattern was not consistent for individual NTD diagnoses. Far East Asians had the highest

Figure 1.— Prevalence of neural tube defects (NTDs) by diagnosis, Hawaii 1986-1997



prevalence of anencephaly (4.31) while Pacific Islanders had the highest prevalence of spina bifida (5.87) and Filipinos of encephalocele (2.17). However, none of the differences between the racial/ethnic groups was statistically significant for any of the diagnostic categories.

Maternal age demonstrated no clear pattern in risk for spina bifida, encephalocele, or all NTDs combined (table 2) although the highest rates for spina bifida and encephalocele were among older women (35-39 and ≥40 age groups, respectively). Anencephaly risk tended to decline with increasing maternal age.

The numbers and rates of NTD-affected pregnancies by county of residence and by metropolitan Honolulu versus the rest of the state are exhibited in table 3 and table 4, respectively. The prevalence for the various diagnostic categories was similar for all counties except for Kauai County, which had a lower prevalence for anencephaly, spina bifida, and total NTDs. Due to the small number of cases, this decreased risk was not statistically significant. The rate was slightly higher for all diagnostic categories except encephalocele for residents of metropolitan Honolulu when compared to the rest of the state.

Table 5 shows the distribution of NTDs by infant/fetus sex. Females were disproportionally represented in all diagnostic categories. This disparity was statistically significant for spina bifida and total NTDs.

Discussion

The total prevalence for NTDs in Hawaii between 1986 and 1997 was 9.95 per 10,000 livebirths and fetal deaths. The prevalence rates for anencephaly and spina bifida were similar (3.62 and 4.51, respectively), while that for encephalocele was substantially lower (1.83). These rates are similar to those observed in other studies

Table 2.— Prevalence of neural tube defects (NTDs) by maternal age, Hawaii, 1986-1997.

Maternal age	No.	Rate*	95% CI**
Anencephaly			
≤19	13	5.65	3.01-9.65
20-24	16	2.64	1.51-4.29
25-29	33	5.03	3.46-7.06
30-34	22	4.24	2.66-6.42
35-39	5	2.12	0.69-4.96
≥40	0	0.00	0.00-8.36
Spina bifida			
≤19	12	5.21	2.69-9.10
20-24	26	4.29	2.80-6.28
25-29	30	4.57	3.08-6.52
30-34	23	4.43	2.81-6.65
35-39	18	7.65	4.53-12.08
≥40	2	4.53	0.55-16.37
Encephalocele			
≤19	3	1.30	0.27-3.81
20-24	12	1.98	1.02-3.46
25-29	17	2.59	1.51-4.14
30-34	7	1.35	0.54-2.78
35-39	3	1.27	0.26-3.72
≥40	3	6.80	1.40-19.86
Total NTDs			
≤19	28	12.16	8.08-17.57
20-24	54	8.91	6.69-11.62
25-29	80	12.18	9.66-15.16
30-34	52	10.03	7.49-13.15
35-39	26	11.05	7.22-16.18
≥40	5	11.34	3.68-26.43

*per 10,000 livebirths. **CI, confidence interval.

Table 1.— Prevalence of neural tube defects (NTDs) by maternal race/ethnicity, Hawaii, 1986-1997.

Race/ethnicity	No.	Rate*	95% CI**
Anencephaly			
white	23	3.67	2.32-5.50
Far East Asian	18	4.31	2.55-6.81
Pacific Islander	23	3.65	2.31-5.48
Filipino	12	2.90	1.50-5.06
Spina bifida			
white	35	5.58	3.89-7.76
Far East Asian	15	3.59	2.01-5.92
Pacific Islander	37	5.87	4.14-8.09
Filipino	15	3.62	2.03-5.98
Encephalocele			
white	13	2.07	1.10-3.54
Far East Asian	8	1.91	0.83-3.77
Pacific Islander	13	2.06	1.10-3.53
Filipino	9	2.17	0.99-4.13
Total NTDs			
white	71	11.32	8.84-14.28
Far East Asian	41	9.81	7.04-13.30
Pacific Islander	73	11.59	9.08-14.57
Filipino	36	8.70	6.09-12.04

*per 10,000 livebirths. **CI, confidence interval.

Table 3.— Prevalence of neural tube defects (NTDs) by county of residence, Hawaii, 1986-1997.

County	No.	Rate*	95% CI**
Anencephaly			
Honolulu	68	3.86	3.00-4.89
Hawaii	10	4.28	2.05-7.86
Maui	7	3.53	1.42-7.27
Kauai	2	1.99	0.24-7.17
Spina bifida			
Honolulu	79	4.48	3.55-5.58
Hawaii	11	4.70	2.35-8.41
Maui	12	6.05	3.13-10.57
Kauai	2	1.99	0.24-7.17
Encephalocele			
Honolulu	34	1.93	1.34-2.69
Hawaii	7	2.99	1.20-6.17
Maui	2	1.01	0.12-3.64
Kauai	2	1.99	0.24-7.17
Total NTDs			
Honolulu	181	10.27	8.83-11.87
Hawaii	28	11.97	7.96-17.30
Maui	21	10.59	6.56-16.18
Kauai	6	5.96	2.19-12.96

*per 10,000 livebirths. **CI, confidence interval.

Table 4.— Prevalence of neural tube defects (NTDs) by urbanity, Hawaii, 1986-1997.

Urbanity	No.	Rate*	95% CI**
Anencephaly			
Metro Honolulu	27	4.04	2.66-5.88
Rest of Hi	60	3.71	2.83-4.77
Spina bifida			
Metro Honolulu	33	4.94	3.40-6.94
Rest of Hi	71	4.39	3.43-5.53
Encephalocele			
Metro Honolulu	13	1.95	1.04-3.33
Rest of Hi	32	1.98	1.35-2.79
Total NTDs			
Metro Honolulu	73	10.93	8.57-13.74
Rest of Hi	163	10.07	8.59-11.74

*per 10,000 livebirths. **CI, confidence interval.

Table 5.— Prevalence of neural tube defects (NTDs) by gender, Hawaii, 1986-1997.

Gender	No.	Rate*	95% CI**
Anencephaly			
Male	26	2.21	1.44-3.23
Female	37	3.32	2.34-4.58
Spina bifida			
Male	39	3.31	2.35-4.53
Female	66	5.93	4.58-7.54
Encephalocele			
Male	17	1.44	0.84-2.31
Female	19	1.71	1.03-2.66
Total NTDs			
Male	82	6.96	5.54-8.64
Female	122	10.96	9.10-13.08

*per 10,000 livebirths. **CI, confidence interval.

conducted in the United States.[4,5,8]

In spite of the relatively small number of cases in a given year, the NTD prevalence demonstrated a general tendency to increase over the twelve-year period of the study. This trend was observed for all of the NTD diagnosis categories and was statistically significant for all NTDs combined. Among the specific NTD types, the increase was lowest for anencephaly (slope = 0.11), greatest for spina bifida (slope = 0.25) and intermediate for encephalocele (slope = 0.12).

This observation runs counter to other recent studies that have reported a decline in NTD prevalence in the United States.[4,5,11,12] A number of these studies did not include electively terminated NTDs in their analysis, while this one does. However, many of these other studies did include time periods prior to when the prenatal diagnosis and elective termination of NTD-affected pregnancies became common practice and/or were able to take into account the impact of elective termination to some degree.

Moreover, since 1992 various recommendations and other actions, including the fortification of "enriched" cereal grains in the U.S. in 1998, have been taken to increase knowledge and consumption of folic acid by women of childbearing age. As a result, NTD rates would be expected to decline since the beginning of the decade. However, neither a reduction in NTD prevalence specifically linked to folic acid use nor more than slight improvements in women's awareness and consumption of folic acid have been reported.[28]

The prevalence trend observed by this study is not believed to be based on biased ascertainment by the HBDP. Since its inception in 1989, the Program's catchment area has not changed, nor has the HBDP significantly modified its birth defects ascertainment procedures for livebirths. The data for years prior to 1989 were collected retrospectively, but the same procedures were applied to these years as for all others.

In 1992, the HBDP stopped systematically reviewing all medical records on fetal deaths less than 20 weeks gestation unless a fetal anomaly was suspected. However, if this change had had any impact on NTD rates it would have been expected to cause a decrease in trend and not an increase. Also, only four of the NTD cases had been identified among fetal deaths less than 20 weeks gestation prior to this change.

In 1993, the HBDP added elective terminations due to fetal anomalies less than 20 weeks gestation to its study criteria. (Prior to this time, only elective terminations 20 weeks or greater gestation were included.) As with livebirth cases, data for earlier years were ascertained retrospectively. Also, the increase in rates continued after this date. Moreover, since the HBDP uses a multiple source ascertainment system to identify cases, it is unlikely that NTD cases of any pregnancy outcome would have been missed by all sources.

A very small number of NTDs were identified by the HBDP prenatally, but the place and date of the end of the pregnancy could not be determined. Since the HBDP has access to all facilities in Hawaii where births and terminations due to fetal anomalies occur, most likely these prenatally-diagnosed pregnancies did not end in the state. Also, they were distributed throughout the twelve-year period of interest and their numbers would be too small to affect the observed trends appreciably.

Nor can the increase be accounted for by an increasing number of non-residents coming to the state to deliver NTD-affected pregnancies. Nine of the NTD cases in the registry occurred to non-residents. While seven of these cases occurred in the second half of the time period under study and only two occurred in the first half, the numbers are too small to account for the observed trend.

The observed increase in NTD prevalence in Hawaii could possibly result from some change in reporting practices by participating facilities, such as a change in defect coding. However, the multiple source system used by the HBDP would tend to minimize the impact of such a change. And to date the researchers have failed to positively identify a change in reporting practices.

The trend may represent a change in demographic patterns among Hawaii's population. However, the only identified change in demographics observed in 1986-1997was a shift toward births to older women. With the exception of anencephaly, this investigation failed to identify any trend in maternal age risk. And for anencephaly, the risk appeared to decrease with increasing maternal age.

Although some variation was observed in the prevalence of NTDs between the racial/ethnic groups examined, the differences were

minor and in no instance statistically significant. Other studies had observed the NTD prevalence to be lower in Asians than whites.[5,7,9] However, these studies grouped Asians together as a single group, thus blurring any differences between the various Asian race/ethnic groups, while this study subdivided this large category. In this investigation, whites did, in fact, demonstrate higher prevalence than Far East Asians for all NTD categories except anencephaly. Pacific Islanders had rates similar to whites, while, with the exception of encephalocele, rates for Filipinos were lower than for whites.

One limitation of this analysis is that a large proportion of the population of Hawaii is of mixed race/ethnicity. For the current analysis, the researchers assigned women of mixed race/ethnicity to a single racial/ethnic group, following the practices of the Hawaii Department of Health. In doing so, racial/ethnic differences may have been blurred. Unfortunately, the researchers cannot identify those cases of mixed-ancestry without reviewing the medical records again. Nor can comparable denominators be easily obtained from the Department of Health.

As mentioned above, anencephaly risk was found to decrease with increasing maternal age, an observation consistent with that of prior studies.[17] Also, this analysis did identify the highest prevalences for spina bifida and encephalocele among the oldest maternal age groups, something which other studies had found.[4,7,17] However, none of these observations was statistically significant.

Aside from encephalocele, NTD risk was much lower in Kauai County, although this observation was not statistically significant. The rates for all NTD categories were similar among the other three counties and similar between metropolitan Honolulu and the rest of the state.

Females were disproportionally more likely to have a NTD than males. The degree of this disparity was not consistent between the types of NTDs: the difference was highest for spina bifida and lowest for encephalocele. The greater prevalence among females observed in this study was in keeping with that found in the literature.[3,6,11,12,18]

The sex of forty-one (17 percent) of the NTD cases in the study could not be determined. Most of these were cases which were electively terminated and there was no mention of the fetus' sex in the medical record. However, sex was not found to affect the decision to electively terminate an NTD-affected pregnancy. Therefore, the cases of unknown sex are not thought to differ significantly from those cases of known sex and affect the sex ratio observed.

The main limitation of this study was its inability to determine a concrete explanation for the apparent increase in prevalence of NTDs in Hawaii between 1986 and 1997. Factors such as changes in case ascertainment over time were eliminated, and, with the possible exception of race/ethnicity, NTDs rates and patterns in Hawaii were similar to those in other parts of the U.S. for the demographic factors studied.

Due to the relatively small number of NTD cases observed by the HBDP each year (11-34), the observed trend may be spurious, in spite of the fact that it passed a test for statistical significance. Only further surveillance and the observation of a continued increase in prevalence would verify the results of this analysis. (And even if the increase does not appear to continue, this would not eliminate the possibility that the observed prevalence increase was true. The factor causing the increase could have ceased to operate or its impact mitigated by some other factor e.g., cereal grain fortification starting in 1998.)

The researchers were restricted in the variables they could examine in an effort to account for the secular increase to those which can be easily and consistently extracted from medical records. These records typically do not contain consistent and detailed information on environmental factors and others such as folic acid consumption, diet, and health behaviors which may affect NTD risk. Such information would perhaps be better obtained through a case-control interview study or some other research methodology. Considering the relatively small number of NTDs which occur each year, a case-control study would likely have to be conducted over a relatively long period of time.

The small number of cases likewise limited the analyses of the other demographic factors. Few of the observed differences in prevalence were found to be statistically significant. Only continued collection of cases over additional years would likely increase the statistical power of such analyses.

In conclusion, NTD rates and demographic factors such as race/ethnicity, maternal age, and sex were analyzed and found to be similar to that observed in other studies in the U.S. This study identified a general increase in the prevalence of NTDs in Hawaii between 1986 and 1997. No concrete explanation for the secular trend could be determined. Further investigation is suggested.

Acknowledgments

We wish to thank Dr. Laurence N. Kolonel, A. Michelle Weaver, and Amy. M. Yamamoto of the Hawaii Birth Defects Program, and the staff of the Office of Health Status Monitoring at the Hawaii State Department of Health.

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Nonmembers.—Please call 536-7702 for a nonmember form. Rates are $1.50 a word with a minimum of 20 words or $30. Not commissionable. Payment must accompany written order.

Office Space

ALA MOANA BLDG.—PHYSICIANS WANTED to share space and support services. Interest in physical rehab. preferred. We have flexible rental arrangements starting at one half-day per week. Run your practice with no fixed overhead. Contact Dr. Speers, REHABILITATION ASSOCIATES, 955-7244.

Wanted

PSYCHIATRIST.— Kaneohe residential Program for adolescents seeks consultant two half-days per month. Schedule, duties, compensation negotiable. Contact Administrator: RAINBOW HOUSE 239-2399.